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Optic Nerve Head Blood Flow Analysis in Patients with Optic Disc Drusen Using Laser Speckle Flowgraphy

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ABSTRACT

Visual field defects are common in patients with optic disc drusen (ODD). Our aim was to examine whether reduced optic nerve head (ONH) microcirculation is related to visual field defects in ODD patients. Vascular and tissue area mean blur rate (MBR_V and MBR_T), measured using laser speckle flowgraphy (LSFG), was significantly lower in the 32 included ODD eyes when compared with 40 healthy eyes (p <.05). There was a moderate correlation between the difference in MBR_T and the perimetric mean defect (R^2 = 0.53) in ODD patients. These findings demonstrate the utility of LSFG in examining ONH blood flow in ODD patients.

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Introduction

Optic disc drusen (ODD) consist of acellular calcified deposits and are seen in the optic nerve head (ONH) of up to 2% of the population.[1,2] Several theories have been proposed as explanations for their emergence, the most prominent being axonal damage leading to increased intracellular calcium deposition in mitochondria.[1]

While most cases of ODD are benign,[3] their occurrence is, occasionally, associated with sudden visual and visual field loss caused by anterior ischaemic optic neuropathy (AION).[4,5] Slowly progressing visual field defects have been widely reported, with prevalences ranging from 49% to 71%.[6,7] Most visual field defects associated with ODD are of nerve fibre bundle origin, but patterns of general constriction and enlarged blind spot have also been reported.[8] Visual field defects tend to occur in patients with visible ODD and are rarely seen in children, where ODD most frequently are deeply buried in the ONH.[6]

Laser speckle flowgraphy (LSFG) is a non-invasive, fast and reliable, quantitative method of measuring ocular blood flow *in vivo*.[9,10] The technique is based on the phenomenon of speckle, which occurs when a diffusing surface is irradiated with laser light.[9] Minuscule differences in the surface create a scatter effect, resulting in a granular pattern viewed by the observer. In vascularized tissue, such as the retina, the choroid, and the ONH, the vessels will become blurred due to the high speed of erythrocytes moving through the lumen. LSFG provides the mean blur rate (MBR), which is automatically calculated from variations in the degree of blurring, as a quantitative index of the blood flow. A decreased MBR thus indicates a reduction in the ocular blood flow of the measurement area.[11]

ONH microcirculation as measured by LSFG has been shown to be reduced in several diseases where damage to the peripapillary nerve fibres is a prominent feature. As such, peripapillary blood flow has been reported to be reduced in patients with glaucoma[12] and autosomal dominant optic atrophy (ADOA).[13]

Decreased blood flow to the ONH may play a role in the pathogenesis underlying ODD-associated visual field defects. Using colour Doppler imaging, it has been shown that ODD patients have low blood flow velocities in the vessels around the ONH and that the blood flow velocity patterns of the central retinal arteries correlated with the extent of the visual field defects.[14] Using optical coherence tomography angiography (OCTA), peripapillary microvascular changes

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correlating with retinal nerve fibre layer and ganglion cell complex reduction have recently been demonstrated in ODD patients compared with healthy controls.[15] To the best of our knowledge, ONH blood flow and microcirculation in patients with ODD have not yet been examined using LSFG.

The objective of this study was to investigate ONH microcirculation in patients with ODD as compared with healthy subjects using LSFG. Additionally, the study aimed to clarify any existing correlation between microcirculation and visual field defects.

Methods

Study population

This case–control study was approved by the institutional review board of the Capital Region of Denmark, project number 2007–58-0015. Informed consent for participation in the research was obtained from each patient and the study adhered to the tenets of the Declaration of Helsinki. Patients with a known diagnosis of ODD were identified from a previous study in the research group and invited to participate in this study. They were included if they had 1) documented ODD in at least one eye on enhanced depth imaging optical coherence tomography using the Optic Disc Drusen Studies Consortium guidelines[16] and 2) documented automated perimetric visual field mean defects of at least −4 dB in at least one eye. Controls were recruited among personnel from the Department of Ophthalmology, Rigshospitalet – Glostrup, Denmark. Participants were excluded if they had the concomitant optic nerve or retinal disease. All patients and controls were examined at the Department of Ophthalmology, Rigshospitalet, between 3rd and 19th December 2018.

Measurement of clinical parameters

All patients had their best-corrected visual acuity (BCVA) measured with the Early Treatment Diabetic Retinopathy Study (ETDRS) chart. Intraocular pressure (IOP) was measured with the Icare TAO1 (Icare, Finland) apparatus, measuring the average of five measurements. Visual field analysis was made retrospectively from existing measurements, using the OCTOPUS 900 (Haag-Streit AG, Koeniz, Switzerland). Visual field measurement of included ODD patients was performed in the period 25th October 2013 to 7th November 2018. Twenty patients were examined using the G-Dynamic testing algorithm. Two patients were examined using the 24–2 program. Both programs used standard white-on-white perimetry. The mean time between visual field testing and LSFG measurement was 10 months and the median time was 4 months.

Blood pressure (SBP: Systolic blood pressure; DBP: diastolic blood pressure; MAP: Mean arterial pressure) was measured three times after 5 minutes of rest using an automated apparatus; the average of these three measurements was then calculated.

Mean ocular perfusion pressure (MOPP) was calculated for each subject as follows:

MOPP = 2/3 MAP – IOP, where MAP = DBP + 1/3 (SBP – DBP)

Laser speckle flowgraphy

ONH blood flow was evaluated using LSFG (LSFG-Retflow, NIDEK Technologies, Aichi, Japan 2018). The principle and methods of LSFG have previously been described in detail.[10,17] Briefly, the instrument consists of a fundus camera equipped with a diode laser (wavelength 830 nm) and a charge-coupled device camera. The main measurement parameter is the MBR. LSFG acquires MBR images of the fundus continuously at a rate of 30 frames per second over a 4 second period. ONH blood flow was analysed by use of the LSFG Analyser software, version 2.14. All examinations were performed by a single operator (J.W.).

Regions of interest were selected using “rubber bands” (Figure 1). These were manually shaped and could be saved for later use (for example, in the same subject). In our case, for each subject, we made a circular rubber band that fitted the optic disc area. Within the ONH, the speckle pattern originates in the large vessel and tissue (capillary) areas of the ONH, which the software “vessel extraction function” divides automatically and measures separately.[18] Hence, MBR is generated

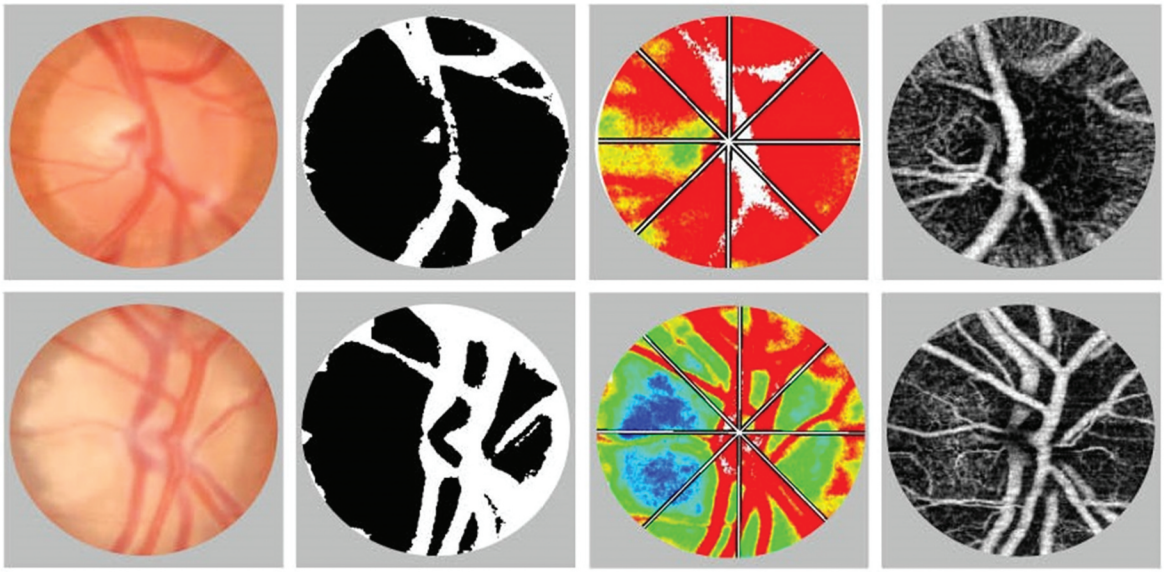

Figure 1. The principle of Laser Speckle Flowgraphy (LSFG) in patients with optic disc drusen (ODD). Upper row: control subject; lower row: ODD patient. First column from left shows an optic disc image of the right eye. Second column shows the first step of image processing in LSFG, vessel extraction. The black area represents the tissue area and the white area represents the vascular area. Third column shows a colour representation of the mean blur rate (MBR), with blue indicating lower values and red and white indicating higher values. The elliptical rubber band is shaped manually to include a region of interest, which can be sub-divided into a total of sixteen parts. Fourth row shows the corresponding optical coherence tomography angiography of the same region.

in all areas of the optic disc, the vessel area of the optic disc (MBR_V), and the tissue area of the optic disc (MBR_T). A composite of these parameters, termed overall MBR or MBR_A, is similarly generated.

Twenty minutes prior to LSFG, and after testing for a relative afferent pupillary defect, the pupils of the enrolled eyes were dilated using topical tropicamide and phenylephrine. As medical dilation of the pupils would interfere with the daily work routine of the control subjects, mydriasis of the control pupils was achieved by dark adaptation over a 10-minute period in the examination room. The pupil was focused in the Iris Viewer, after which the light intensity was adjusted to an appropriate level on the measurement screen. A total of four measurements were recorded for each subject's eye, and the mean of these measurements was used for later analysis.

Statistical analysis

For each variable, the FREQUENCY function in Microsoft Excel was used in order to assess whether the material displayed a Gaussian distribution. If this was the case, F-test and Student's T-test were performed using the FTEST and TTEST functions in the aforementioned software.

For multivariate analysis, non-parametric statistical analysis was performed using SAS statistical software (SAS 9.4; SAS Institute, Cary, NC, USA). Wilcoxon two-sample test was used for data that were not normally distributed. Age adjustment of the data was performed using mixed model analysis.

Results

A total of 23 patients (46 eyes) with bilateral ODD and 20 healthy controls (40 eyes) were examined. Out of the 46 eyes with ODD we included 32 eyes from 22 ODD patients. Two eyes were excluded due to concomitant retinal disease (retinitis pigmentosa), while the remaining 12 eyes were excluded due to having a visual field perimetric mean defect below the inclusion cut-off. No controls were aware of any eye disease at the time of the study, and no controls were thus excluded. Visual acuity was significantly better in the control group than in the patient group (−0.09 ± 0.16

Table 1. Demographic and ocular characteristics of patients with optic disc drusen and healthy controls. ODD: optic disc drusen; IOP: intraocular pressure; MOPP: mean ocular perfusion pressure; MBR_T: mean blur rate of tissue area; MBR_V: mean blur rate of vascular area; MBR_A: overall mean blur rate.

	Control	ODD	p-value
Number of eyes	40	32	
Gender (M: F)	8: 12	10:12	.72
Age (years)	40 ± 13	54 ± 19	.02
Visual acuity (logMAR units)	−0.09 ± 0,16	0.14 ± 0.30	<.05
Spherical equivalent (dioptres)	−0.76 ± 2.34	1.1 ± 3.3	<.05
IOP (mmHg)	14 ± 3.4	15 ± 3.5	.24
MOPP (mmHg)	50.8 ± 6.0	52.1 ± 6.6	.38
MBR_T (arbitrary units)	16.9 ± 4.5	13.6 ± 4.5	.03
MBR_V (arbitrary units)	61.9 ± 11.5	43.5 ± 12.2	<.05
MBR_A (arbitrary units)	28.6 ± 5.9	21.2 ± 6.3	<.05

logMAR versus 0.14 ± 0.30 logMAR, $p < .05$). Age was significantly higher (54 ± 19 years versus 40 ± 13 years, $p = .02$) in the patient group; the overlap was, however, large. There was no significant difference in intraocular pressure between the patient and the control groups. The characteristics of the two groups are presented in Table 1.

Non-parametrical analysis of the MBR in controls and study patients showed significantly lower MBR_T (13.6 ± 4.5 arbitrary units [AU], $p = .03$) and MBR_V (43.5 ± 12.2 AU, $p < .05$) in ODD patients. These observations remained significant, when adjusting for age. Association between MBR_T and MBR_V was stronger in ODD patients, as compared with healthy subjects ($R^2 = 0.74$ and $R^2 = 0.51$, respectively).

MOPP was slightly increased in ODD patients (52.1 ± 6.6 mmHg versus 50.8 ± 6.0 mmHg in controls) but the difference was not significant.

The visual field mean defect of the enrolled ODD patients was −12.2 ± 5.2 dB. The association between MBR_T and perimetric mean deviation (MD) was weak (R^2=0.14), as was also the case for MOPP and MBR_V. Post-hoc analysis showed that the difference in MBR_T between eyes in the same subject was moderately correlated to the difference in perimetric MD (R^2=0.45). When comparing the difference in MBR_T and perimetric MD between "healthy" eyes with ODD (perimetric MD > −4 dB) and their "unhealthy" counterparts (perimetric MD < −4 dB), the correlation was even stronger (R^2=0.53) (see Figure 2). The corresponding

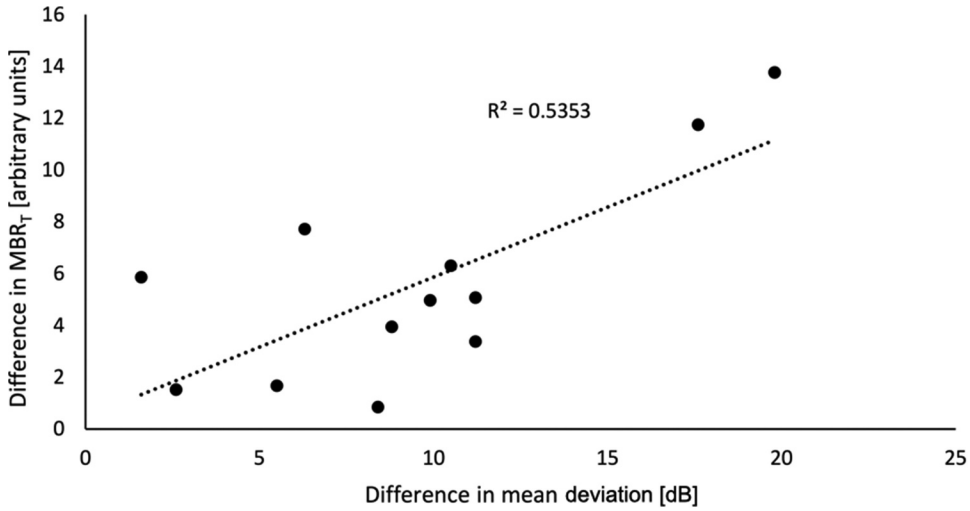

Figure 2. Difference in the mean blur rate in the tissue area of the optic disc (MBR_T) in optic disc drusen patients with visual field mean deviation below −4 dB in one eye and above −4 dB in the fellow eye as a function of the difference in perimetric mean deviation between the two eyes.

correlation for MBR_V was weaker, but still moderate (R^2=0.27).

Discussion

The aim of this study was to examine the ONH microcirculation using LSFG in subjects with ODD, as compared with healthy subjects. Our hypothesis was that ODD patients with visual field defects exhibit impaired ONH microcirculation, as shown using LSFG in other optic neuropathies, such as glaucoma[19] and ADOA.[13]

We found that MBR_T and MBR_V were significantly decreased in ODD patients, as compared with healthy controls. Furthermore, we found a positive correlation between ONH microcirculation (as represented by MBR_T), intravascular flow in ONH vessels (as represented by MBR_V) and visual field defects. The association was stronger when comparing affected ODD eyes with the unaffected fellow eye, as opposed to pooling the data from all affected eyes. This may be attributed to the large variance in MBR, which is true for both ODD patients and control subjects (SD 4.5 AU in MBR_T for both groups; 11.5 AU for controls and 12.2 AU for ODD patients in MBR_V, see Table 1).

As MBR_T is believed to reflect the blood flow in the ONH tissue supplied by the short posterior ciliary arteries,[20] our findings suggest a relatively selective impairment of this circulatory system. One may speculate as to why this system should be affected by the presence of ODD. As these are minuscule vessels, sheer mechanical compression could be a plausible explanation, as has been stated as a putative cause for ODD-associated AION.[21] This is in accordance with visual field defects in ODD patients being most commonly observed with older age, when ODD is frequently larger and more visible.[6]

In a study of non-arteritic AION in a rodent model, peripapillary circulation, as measured by LSFG, was shown to be significantly reduced.[22] This has also been shown in human subjects with optic disc melanocytoma, where presumed compression resulted in visual field defects, in a somewhat similar manner to ODD.[23]

An earlier study has shown a correlation between visual field defects and intravascular flow velocity in the central retinal artery in ODD patients using colour Doppler imaging.[14] Our study corroborates this, as MBR_V was significantly reduced in ODD patients (43.5 ±12.2 AU; 61.9 ±11.5 AU). Mechanical compression of the major vessels of the ONH seems to be the most plausible explanation in this case as well.

Our study had some limitations that need consideration. Overall, we found higher values of MBR_T than in comparable studies.[13,19] As LSFG is still not a commonly used method of examining ocular circulation in the western hemisphere, most comparable results are to be found in Japanese studies. This may present obstacles with regards to the analysis of our results. The discrepancies between our results and the aforementioned may be explained by the use of different equipment, but possibly also by differences related to ethnicity. Our results are, however, consistent with the existing, albeit few, LSFG studies on Caucasian subjects.[24–26]

The significant difference in age between the groups also limits the comparison between patients and controls. Our results remained significant after statistical age adjustment by mixed model analysis, suggesting that this not a determining factor in the difference between the groups.

Another possible limitation may be the nature of the very disease that has been examined in this paper. The presence of drusen may in itself be part of the explanation as to why MBR_T and MBR_V are decreased in ODD patients, as this may be due to blockage of the laser signal used to measure LSFG. It would however not seem plausible to observe the large differences in MBR_T when comparing ODD eyes in the same patient (as is illustrated in Figure 2), if this was the entire explanation. Future studies may include volumetric measurement of ODD to assess this effect.

Decreased ONH microcirculation may also be due to axonal nerve fibre loss, as seen in the previously mentioned studies of ADOA and glaucoma. Correlating LSFG values with retinal nerve fibre layer thickness could be considered in future studies.

In conclusion, this study showed a reduced blood flow within ONH vessels and in the peripapillary tissue area in ODD patients with visual field defects using LSFG. Future studies in larger

patient cohorts are needed, and the method would benefit of a comparison to other methods of ONH blood flow evaluation such as OCTA.

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